Clinical and Pathologic Study of Canine Lymphoma: Clinical Staging, Cell Classification, and Therapy [1,2]

Robert A. Squire, *D.V.M.*, Mitchell Bush, *D.V.M.*, Edward C. Melby, *D.V.M.*, Lena May Neeley, *and* Barbara Yarbrough,[3] *Division of Animal Medicine and Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205*

SUMMARY—A prospective study of 100 naturally occurring canine lymphomas was conducted. All lymphomas were clinically staged and pathologically classified according to criteria used in human patients. Four chemotherapy schedules were evaluated, and animals were monitored constantly. Percent remissions, mean remission durations, and survival times were correlated with clinical stages, cell classification, and therapy schedules. Most dogs presented in stage III, classified histologically as undifferentiated or stem-cell types, with fine chromatin patterns in fresh imprints. The histiocytic type and stippled chromatin pattern were second most frequent pathologic classifications, and this group generally had the highest percent remissions and the longest mean survival periods. The highest percent remissions (79%) and the longest mean remission durations (184 days) were achieved with combined vincristine-cyclophosphamide-prednisone therapy, regardless of clinical stage or cell type. There was no correlation between clinical staging and cell classification, and cell types did not vary with tumor location or disease progression. Bacterial sepsis and drug toxicity were the major causes of death, and splenectomies performed in 21 dogs reduced survival times. The value of canine lymphomas as models for clinical studies of non-Hodgkin's lymphomas was discussed.—J Natl Cancer Inst 51: 565–574, 1973.

LYMPHOMAS are among the most frequent naturally occurring tumors in dogs; Dorn et al. reported an estimated annual incidence of 24/100,000 population (*1*). They are exceeded in frequency only by tumors of the mammary glands and skin. The major clinical and pathologic features of lymphomas were well documented (*2–9*), and therapeutic results were reported (*10–14*). It is uncertain whether a true Hodgkin's-like disease occurs in dogs, but reports in the literature describe cases with striking morphologic resemblance to Hodgkin's disease, mixed cell type (*7, 9*). The etiology of canine lymphomas is not known. Several tumors have been transmitted with cells (*15–18*), but cell-free transmission has been unsuccessful. Although most experimental animal studies in cancer therapy used small laboratory rodents, their size, genetic makeup, and the acute nature of their diseases made it difficult to apply results to human patients. Naturally occurring cases of canine lymphoma, on the other hand, are excellent models for clinical investigations (*19–21*). The size, random breeding, and tractability of dogs and the slow, progressive nature of the tumors allow affected animals to be evaluated and treated like human patients. Additional advantages are that dogs share man's environment and are usually allowed to live out their lifespans.

Although non-Hodgkin's lymphomas in man are usually classified cytologically, only one report (*22*) correlates clinical disease with the cell classification of Rappaport. Many persons with non-Hodgkin's lymphomas present in more advanced stages of disease than do Hodgkin's patients. Extranodal sites are often involved, and leukemia also occurs in some cases. These parameters have not been adequately considered in evaluating clinical trials in human patients. The interrelation-

[1] Received January 31, 1973; accepted April 25, 1973.

[2] Supported in part by Public Health Service research grants RR00130 and RR05010 from the Division of Research Resources, and American Cancer Society grant IN-11.

[3] We gratefully acknowledge the preparation of illustrations by Mr. Raymond Lund and the secretarial assistance of Ms. Linda DePalo.

504-843—73——16

ships, if any, between clinical staging, cell classification, specific drug efficacies, and survival are not certain. Carbone recently indicated the need for considering these additional factors in evaluating clinical trials (*23*).

Since the dog is a suitable animal model, a prospective clinicopathologic study of naturally occurring canine lymphomas was conducted to evaluate these parameters. The diseases were clinically staged and pathologically classified according to criteria used in human lymphomas (*24*, *25*), and several chemotherapeutic schedules were evaluated. Animals were followed throughout their diseases, and remissions and survival times documented. This report summarizes data for the first 100 dogs in which complete clinical and pathologic evaluations were performed.

MATERIALS AND METHODS

Patients.—The 48 males and 52 females were privately owned dogs with naturally occurring lymphomas, and were referred to our study by practicing veterinarians in the Baltimore-Washington area. Twenty-eight females had been sterilized by ovariohysterectomy between the ages of 6 months and 1 year. The mean age of the dogs was 8 years (range, 3-16 yrs). Many breeds were represented, but German shepherds and boxers were most frequent.

Owners agreed to necessary surgery, hospitalization, weekly follow-up visits, and final necropsy. They also administered medicine and provided close observation at home as required throughout the disease. Since all the dogs were pets, nontreatment controls were not available.

Clinical evaluation and staging.—On presentation, each animal was given a complete physical and hematologic examination, including chemistries for liver, kidney, and pancreatic function. Urinalysis, fecal analysis, and radiologic examination of the thorax and abdomen were also performed. All peripheral nodes and other tumor masses were measured two-dimensionally, and when possible, three-dimensionally. Bone-marrow smears were taken from the iliac crest. In 21 dogs, exploratory laparotomies and splenectomies were performed at the time of admission. These were done when owners permitted, and not on the basis of clinical findings.

Tumor measurements and peripheral blood examinations were made daily to weekly during intensive therapy. In this study, leukemic peripheral blood was defined as >35% lymphocytes in the differential count, with a majority of neoplastic cells. The recognition of neoplastic cells was rarely equivocal; when present they were always numerous and were atypical for canine blood (fig. 1). Nuclei were large and sometimes distorted. Nucleoli were prominent and chromatin was fine or stippled without blocky condensation. In no instance was there an elevated lymphocyte count without a large percentage of obviously neoplastic cells, and in only 2 cases was there leukemia with <35% lymphocyte count. Both of these animals, however, had absolute lymphocytosis, and >90% of the lymphocytes were neoplastic. Marrow involvement was considered positive if neoplastic cell foci were found or if lymphocytes exceeded 10% of the nucleated cells. All these evaluations were the basis of the clinical staging outlined in table 1.

Pathologic examination.—An involved lymph node with capsule intact was removed in every case. In most instances fresh, air-dried tumor imprints were prepared from cut surfaces, fixed in absolute methanol, and stained with May-Grünwald Giemsa. The node was then sliced into maximum thicknesses of 0.5 cm and fixed immediately in 10% neutral buffered formalin. Paraffin-embedded sections were cut at 6μ and stained with hematoxylin and eosin (H & E).

Tumors were classified independently by examination of tissue sections and fresh imprints. Tissue sections were classified similar to the method of Rappaport (*25*) as undifferentiated or stem cell, histiocytic, lymphocytic poorly differentiated, lymphocytic well-differentiated, or mixed lymphocytic-histiocytic. Each was also subclassified as diffuse or nodular.

The undifferentiated lymphomas (fig. 2) were predominantly cells with delicate nuclea ;membranes which were round-to-oval or slightly indented. Nucleoli were small and distinct, and chromatin particles and strands were prominent. Cytoplasm was indistinct and faintly stained. Scattered macrophages with clear cytoplasm and intracytoplasmic cellular debris ("starry sky") were sometimes numerous.

Histiocytic lymphomas (fig. 3) were the largest cell type. Nuclei were rounded to irregular with delicate nuclear membranes and large, often single, "bull's-eye" nucleoli. Chromatin strands connected the nucleoli and nuclear membranes. Cytoplasm was more abundant than in other cell types, often with indistinct margins, and was eosinophilic to amphophilic. Phagocytosis of cell debris by tumor cells was occasional, and non-neoplastic macrophages were also numerous as in the stem-cell type.

TABLE 1.—*Clinical staging of canine lymphomas*

Stage*	Description
I	Involvement limited to one lymph node or group of nodes in one anatomic region.
II	Involvement of multiple lymph nodes but limited to one side of diaphragm.
III	Generalized involvement but limited to lymphoid tissues, i.e., lymph nodes, spleen, tonsils, thymus.
IV	Involvement of any nonlymphoid tissues including viscera, blood, bone marrow, central nervous system, eyes, etc.

*Each stage was subclassified A (none-to-slight systemic signs—mild fever, anorexia, lethargy, and normal clinical chemistries) or B (severe systemic signs—weight loss, anemia, leukopenia, vomiting, diarrhea, and abnormal clinical chemistrie).

The lymphocytic, poorly differentiated type (fig. 4) consisted predominantly of cells somewhat larger than small lymphocytes. Nuclear membranes were coarse and irregular or twisted in outline; nucleoli were small and prominent. Nuclear chromatin was minimal and cytoplasm was scant and poorly visualized. No mixed lymphocytic-histiocytic or lymphocytic well-differentiated types were seen.

Imprints were classified according to the predominant chromatin patterns as either fine, stippled, or coarse. The fine chromatin pattern (fig. 5) had a homogeneous ground-glass or finely particulate appearance. The cytoplasm was a distinct basophilic rim, and the nucleus was central or eccentric. Cells with stippled chromatin (fig. 6) were large, with broad or indistinct cytoplasm. Chromatin particles were coarse and prominent. The coarse chromatin pattern (fig. 7) was characterized by distinct condensations or clumping of chromatin material, and the cells were smaller than the preceding cell types.

In several animals repeat biopsies were performed during the diseases, both during remission and exacerbations. All animals were completely necropsied immediately after death. Some animals were killed in terminal illness by intravenous sodium pentobarbital for humane reasons or at the request of owners.

Treatment and evaluation of response.—Animals were hospitalized or examined weekly throughout therapy, and hematologic values were monitored daily to weekly as necessary. Specific and supportive therapy for drug side-effects and other clinical problems was administered as necessary: antibiotic therapy, blood transfusions, fluid therapy, stomach-tube or intravenous feeding, and special diets. Antibiotics were administered when specific infection was known or suspected, if fever developed, or if the total leukocyte count dropped below 1000/mm^3. Until blood or other cultures and sensitivities could be evaluated, tetracycline, chloramphenicol, and ampicillin were used most frequently. Specific tumor therapy included prednisone (P), cyclophosphamide (C, Cytoxan, Mead Johnson Co.), vincristine (V, Oncovin, Eli Lilly and Co.), and 6-mercaptopurine (6MP, Purinethol, Burroughs-Wellcome Co.), alone and in combinations and sequences. Chemotherapy schedules are summarized in table 2. Most animals that were treated first with only P or PC were subsequently given the VCP regimes if response was unsatisfactory or when refractoriness developed.

Schedule 4 (VCP-6MP) was the initial treatment given to 27 dogs. Maximum clinical remissions were always observed by the 14th day, regardless of treatment, and were then recorded as follows: complete—no detectable tumor masses and no blood or marrow involvement; partial—50% or greater, but less than complete, reduction in tumor sizes and blood and marrow involvement; unsatisfactory—no change or less than 50% reduction.

Mean objective remission durations were the number of days before a given regime failed to maintain complete or partial remission in spite of drug-induced toxicity. This was usually manifested as severe myelosuppression and gastrointestinal disturbances. Survival was the number of days from initial presentation until natural death or euthanasia administered in terminal disease. Eighteen animals died or were euthanized within 14 days of admission, usually because of advanced disease and unsatisfactory response to therapy. These 18 animals were not included in survival or remission-duration studies.

TABLE 2.—*Chemotherapy schedules for canine lymphomas*

Schedule	Drug and dosage
1	P: 2.0 mg/kg/day orally for 7 days; 1.0 mg/kg/day thereafter.
2	P: as above; plus C*: 5.0 mg/kg/day orally for 7 days; 2.5 mg/kg/day thereafter.
3	Repeat every 14 days—V*: 0.030 mg/kg intravenously on day 1; P: 1.0 mg/kg/day orally on days 1–7; C*: 5.0 mg/kg/day orally on days 2–7.
4	Repeat every 30 days—V*: 0.030 mg/kg intravenously on days 1 and 8; P: 2.0 mg/kg/day orally on days 1–8, then 1.0 mg/kg/day orally on days 9–21; C*: 5.0 mg/kg/day orally on days 15–21; 6MP*: 5.0 mg/kg/day on days 15–21.

*Not administered if white blood cells <4,000/mm^3.

RESULTS

Staging and Pathologic Classification

Of the 100 animals, 96 were presented in stages III or IV, with the majority in stage IIIA (table 3). Generalized, painless lymphadenopathy was the most common presenting sign, and approximately one-fourth of the animals had splenomegaly. All dogs in stage III had lymph node involvement on both sides of the diaphragm; therefore, spleen or other lymphoid involvement was not necessarily a determining factor in this classification scheme. Dogs were classified as stage IV mostly because of peripheral blood or bone marrow involvement. Twenty-eight dogs presented with leukemia, and 32 with marrow involvement. These correlated in all but 6 cases. Some also had enlarged livers, and a few had involvement of other sites, e.g., eyes, spinal canal (epidural space), intestines, mediastinum, and in one case, facial bones. No meningeal or other brain involvement was recognized initially and only 4 animals had small meningeal infiltrates at necropsy.

Most tumors were classified as undifferentiated (stem-cell) type in sections stained with H & E and had fine chromatin patterns in imprints (table 3). Histiocytic tumors and stippled chromatin patterns were the second most frequent types; few were the lymphocytic, poorly differentiated type or had coarse chromatin patterns in imprints. No lymphocytic well differentiated or mixed lymphocytic-histiocytic types were present in these 100 cases. Only 1 nodular pattern was found, all others being diffuse. There was partial correlation between fixed section and imprint classifications. All stem cells had a fine chromatin pattern, and many histiocytic types had a stippled chromatin pattern. A few histiocytic types had fine chromatin patterns and were indistinguishable from stem cells in imprints. Poorly differentiated lymphocytic types all had coarse chromatin patterns.

Multiple biopsies at the time of admission never revealed variation in cell type at different sites. Neither did repeated pathologic examinations or necropsies demonstrate change to a different cell classification.

Response to Therapy Schedules

Mean durations of remissions according to treatment are presented in table 4. Schedule 1 (P) produced complete remission in 20 of 49 animals, with a mean objective remission duration of 53 days. Remission induction was rapid and usually reached its maximum in 7 days, but was often partial within 72 hours. Schedule 2 (PC) produced complete remission in 13 of 34 dogs, and the mean objective remission duration was 62 days. When tumor growth was noted while the dog was on the maintenance C dose of 2.5 mg/kg, the 5.0 mg/kg level administered for 5–7 days often induced complete remission again. Twenty-five animals had previously received P therapy alone, and those responsive to P alone were usually equally responsive to PC combinations, even though they had all become refractory to the single agent. Seven that failed to achieve remission with P alone showed sensitivity to PC, and only 2 animals failed to respond to PC after complete remission with P alone. Schedule 3 (VCP) was administered to 19 animals, and 15 achieved complete remission within 2 weeks. The mean duration of objective remission was 184 days Fourteen of the 19 animals had previously been treated with P or PC and had shown unsatisfactory response or become refractory. Of these 14 animals, 12 achieved complete remission with the PCV combination. Schedule 4 (VCP-6MP) produced complete remission in 19 of 25 animals, and none had prior tumor therapy. The mean duration of objective remission was 136 days.

Clinicopathologic Correlations

The mean survivals according to clinical stages are presented in table 5. A difference was notable

TABLE 3.—*Clinical stages and cytologic classifications of 100 canine lymphomas**

Clinical stage	Number of dogs	H & E section			Fresh imprint†		
		U	H	LPD	F	S	C
I:							
A	0	0	0	0	0	0	0
B	2	1	1	0	1	1	0
II:							
A	2	2	0	0	1	0	1
B	0	0	0	0	0	0	0
III:							
A	44	26	15	3	34	5	3
B	17	10	6	1	7	4	1
IV:							
A	20	11	8	1	16	1	3
B	15	9	5	1	8	5	2
Total	100	59	35	6	67	16	10

*Abbreviations: U, undifferentiated; H, histiocytic; LPD, lymphocytic poorly differentiated; F, fine chromatin pattern; S, stippled chromatin pattern; C, coarse chromatin pattern.

†Available in only 93 cases.

between stages III and IV, which included most cases with a longest mean survival of 160 days in stage IIIA. There was no correlation between clinical staging and objective tumor response to the various treatment schedules or to cell classifications.

Table 6 illustrates the percent of complete remissions according to treatment schedules and cell classifications. The histiocytic and stippled chromatin pattern types achieved the highest percent of complete remissions with schedules 2–4. Correlation was not obvious between sensitivity to specific schedules and tumor cell types.

The mean survival of the 2 predominant cell types was calculated with dogs only in clinical stage IIIA (the largest group), to eliminate the initial extent of disease as a variable (table 7). The histiocytic and stippled chromatin types appeared to have the longest survival, but the results may not be significant in either classification ($P>0.05$).

Since many dogs received more than 1 treatment schedule during their diseases, no correlations between survivals and treatments were made. Splenectomy appeared to reduce length of survivals. Twelve dogs in stage IIIA had been splenectomized and treated with schedules 3 or 4, and had a mean survival of 104 days. In contrast, 13 intact dogs which received similar therapy and also presented in stage IIIA had a mean survival of 164 days. Approximately one-third of each group had tumor involvement of their spleens.

TABLE 4.—*Mean objective remission durations according to chemotherapy schedules**

Treatment schedule	Number of animals treated	Percent in remission	Remission (days)
1	49	41	53(14–210)
2	34	38	62(17–130)
3	19	79	184(30–282)
4	25	76	136(18–300)

*Includes only animals surviving at least 14 days.

TABLE 5.—*Mean survival according to clinical stage**

Clinical stage	Number of animals	Percent complete remission	Survival (days)
I:			
A	0	—	0
B	2	100	136. 5(32–241)
II:			
A	2	50	263. 5(252–272)
B	0	—	0
III:			
A	35	77	160(14–368)
B	14	50	90(14–278)
IV:			
A	18	67	71. 8(14–202)
B	11	64	64. 6(15–178)

*Includes only animals surviving at least 14 days.

Toxicity

No severe side-effects were noted with P therapy except in 1 dog, which developed a gastric ulcer after several months of therapy. In several instances polyuria and polydypsia necessitated reduction of the dosage to 0.25–0.5 mg/kg/day. Increased appetite and mild signs of Cushing's syndrome were noted in several animals.

C and P induced only moderate leukopenia and anemia in most dogs. The leukocyte count rarely

TABLE 6.—*Percent complete remissions according to cell classification and treatment schedules*

Cell classification*	Schedule 1		2		3		4	
	Number of animals	Percent complete remission	Number of animals	Percent complete remission	Number of animals	Percent complete remission	Number of animals	Percent complete remission
H & E section:								
U	33	42	20	35	10	80	15	40
H	12	33	11	54	7	86	11	91
LPD	4	50	3	0	2	50	1	100
Fresh imprint:								
F	33	43	24	42	12	67	18	72
S	9	33	3	67	3	100	5	80
C	5	40	5	20	4	75	2	50

*For definitions of abbreviations, *see* footnote, table 3.

TABLE 7.—*Mean survivals of dogs presenting in stage IIIA according to cell classifications**

Cell classification	Number of animals	Survival (days)
H & E section:		
Undifferentiated	21	88(24–278)
Histiocytic	14	132(14–368)
Fresh imprints:		
Fine chromatin pattern	26	104(17–368)
Stippled chromatin pattern	6	121(51–307)

*Includes only animals surviving at least 14 days.

dropped below 4000/mm^3, and thrombocytopenia was not seen. Gradual loss and discoloration of hair and a few cases of hematuria were noted, and 1 animal died of hemorrhagic bullous cystitis. C was stopped whenever hematuria occurred, and chloramphenicol or sulfasoxasole therapy was administered until urine cultures and sensitivities were evaluated.

VP therapy alone was well tolerated and few animals developed more than transient anorexia, moderate leukopenia, and anemia. The VCP combination or the C-6MP phase of schedule 4 regimes was quite toxic, and many animals showed leukopenia, gastrointestinal disturbances, and sometimes anemia. Leukocyte counts frequently were $<$4000/mm^3, and a few cases were $<$1000/mm^3. Thrombocytopenia slightly $<$100,000/mm^3 occurred in only 4 animals, and no bleeding diatheses developed.

Most dogs that received only schedules 1 or 2 died or were killed because of widely disseminated tumors refractory to treatment. Bacterial septicemias were the major cause of natural deaths in dogs receiving the more intensive schedules 3 and 4. Terminal fevers were common and cultures of urine, feces, blood, and spleens yielded mainly gram-negative coliform bacteria. *Pseudomonas* was cultured from the urinary tract of 1 dog, and no mycotic or protozoan infections were recognized.

DISCUSSION

This study used naturally occurring lymphomas in dogs as animal models for clinical investigations. It was determined that clinical staging and pathologic classification according to criteria for human patients may be applied, and that response to therapy is approximately equivalent.

Spontaneous remissions have not been reported in canine lymphomas, but untreated survival times are difficult to establish with certainty. The time of onset of disease is usually vague and depends on the owners first noticing prominent lymphadenopathy. Furthermore, most animals are euthanized after diagnosis. From histories of our cases which were first presented in terminal disease, we estimate that untreated dogs survived approximately 2–6 months. This agrees with an earlier study, which reported average survivals of 99 days (*2*). Survival and remission durations following treatment are not comparable to the human diseases, perhaps because of biologic differences between species, but also because of the relative lack of sophistication and experience in canine clinical oncology (including supportive care) and the fact that many animals are first presented for treatment in advanced stages of the disease. However, evaluations of therapy and management and pathologic or cytologic correlations are readily performed and perhaps equatable to the human patient.

As in human lymphomas, dogs with more advanced clinical stages in this study had shorter survivals. There was no correlation of clinical stages and degree of tumor sensitivity to various drugs, nor was there correlation between clinical stages and cell classifications.

The incidences of cell and pathologic classifications varied from those reported in human diseases. Only 1 nodular pattern was noted, but this may reflect failure of pet owners to recognize earlier stages of disease if the nodular pattern often progresses to a diffuse form. Most tumors were undifferentiated (stem cell) or histiocytic types, and only 6 were the lymphocytic poorly differentiated type. No change or variation in cell types occurred in any case, regardless of tumor location or progression.

Correlations between cell classification and response to specific drug regimes were not readily apparent. Continuous administration of P alone or with C (schedules 1, 2) were the least effective, regardless of cell type. Intermittent, more intensive, combined therapy was most effective and, irrespective of all other factors, the combined VCP

sequences (schedule 3) induced the greatest percentage of complete remissions and the longest objective remission durations. This correlates with observations in human patients, in which various combinations of these 3 drugs have been highly successful (*23*). V, a metaphase arrester, was administered 24 hours before C was started, which perhaps resulted in a larger population of S phase synchronized cells sensitive to C. Schedule 4 (administrations of VP with C-6MP) which was started several days later, appeared less effective.

It was suggested that tumors of histiocytic types were equally or more sensitive to intensive combined therapy than were stem-cell types. The mean survival of the histiocytic type was also longest, but not statistically significant. This does not compare with the poorer prognosis often attributed to reticulum cell sarcomas in man; however, cytologic criteria have not always been consistent or well defined. In this study, not all tumors classified as histiocytic in tissue sections appeared as the same cell type by the imprint method. Furthermore, clinical response and/or survival in non-Hodgkin's lymphomas in man have often not considered clinical stages or involvement of extranodal sites. These factors probably influence the clinical response and prognosis to an equal or greater extent than the predominant cell type.

Tumor remissions were achieved more rapidly in the dogs than in most human patients with non-Hodgkin's lymphomas. Nearly all tumors were of poorly differentiated cell types, and mitotic figures were usually numerous. These observations suggest that many cells in the canine tumors were in the growth fraction, a situation more analogous to human Burkitt's lymphoma or acute lymphocytic leukemia, both of which are highly sensitive to chemotherapy.

Splenectomy had an adverse effect on longevity, when mean survivals between closely matched groups of dogs were compared. Since bacterial infections were a major cause of deaths in these cases, immunologic impairment in the splenectomized patients may have been an important factor.

Although this study lacked the resources and sophistication of human patient evaluation and treatment, it demonstrated the value of naturally occurring tumors in larger animal models for clinical-pathologic studies. Some of our preliminary results may help to evaluate human patients with non-Hodgkin's lymphomas. Other areas, particularly tumor immunology and immunotherapy, could also be readily explored in dogs, since the lack of known specific tumor etiology and antigens in canine lymphomas is analogous to the situation in most human patients.

REFERENCES

(*1*) Dorn CR, Taylor DO, Hibbard HH: Epizootiologic characteristics of canine and feline leukemia and lymphoma. Am J Vet Res 28:993–1001, 1967

(*2*) Bloom F, Meyer LM: Malignant lymphoma (so-called leukemia) in dogs. Am J Pathol 21:683–703, 1945

(*3*) Meier H: Neoplastic diseases of the hematopoietic system in the dog. Zentralbl Veterinaermed [A] 4: 633–688, 1957

(*4*) Smith HA: Malignant lymphoma in animals. Am J Clin Pathol 38:75–87, 1962

(*5*) ———: Leukemic neoplasia in the dog. Ann NY Acad Sci 108:633–641, 1963

(*6*) Van Pelt RW, Conner GH: Clinicopathologic survey of malignant lymphoma in the dog. J Am Vet Med Assoc 152:976–989, 1968

(*7*) Squire RA: Hematopoietic tumors of domestic animals. Cornell Vet 54:97–150, 1964

(*8*) ———: A cytologic study of malignant lymphoma in cattle, dogs and cats. Am J Vet Res 26:97–107, 1965

(*9*) ———: Spontaneous hematopoietic tumors in dogs. Natl Cancer Inst Monogr 32:97–116, 1969

(*10*) Moldovanu G, Friedman M, Miller DG: Treatment of canine malignant lymphoma with surgery and chemotherapy. J Am Vet Med Assoc 148:153–156, 1966

(*11*) Old LJ, Boyse EA, Campbell HA, et al: Treatment of lymphosarcoma in the dog with L-asparaginase. Cancer 20:1066–1070, 1967

(*12*) Brick JO, Roenigk WJ, Wilson GP: Chemotherapy of malignant lymphoma in dogs and cats. J Am Vet Med Assoc 153:47–52, 1968

(*13*) Squire RA, Bush M: Malignant lymphoma in dogs. *In* Current Veterinary Therapy, 4th ed. (Kirk RW, ed.). Philadelphia, WB Saunders Co., 1971, pp 271–276

(*14*) McCelland RB: Chemotherapy in reticulum-cell sarcoma in five dogs and a cat and in mast-cell leukemia in a cat. Cornell Vet 61:477–481, 1971

(*15*) Moldovanu G, Moore AE, Friedman M, et al: Cellular transmission of lymphosarcoma in dogs. Nature (Lond) 210:1342–1343, 1967

(*16*) CHAPMAN AL, BOPP WJ, BRIGHTWELL AS, et al: Preliminary report on virus-like particles in canine leukemia and derived cell lines. Cancer Res 27:18–25, 1967

(*17*) KAKUK TJ, HINZ RW, LANGHAM RF, et al: Experimental transmission of canine malignant lymphoma to the beagle neonate. Cancer Res 28:716–723, 1968

(*18*) COHEN H, CHAPMAN AL, EBERT JW, et al: Cellular transmission of canine lymphoma and leukemia in beagles. J Natl Cancer Inst 45:1013–1024, 1970

(*19*) JOHNSON RE, CAMERON TP, KINARD R: Canine lymphoma as a potential model for experimental therapeutics. Cancer Res 28:2562–2564, 1968

(*20*) SQUIRE RA, MELBY EC JR: Naturally occurring canine and feline lymphomas as biomedical models. Natl Acad Sci Publication no. 1594:3–12, 1968

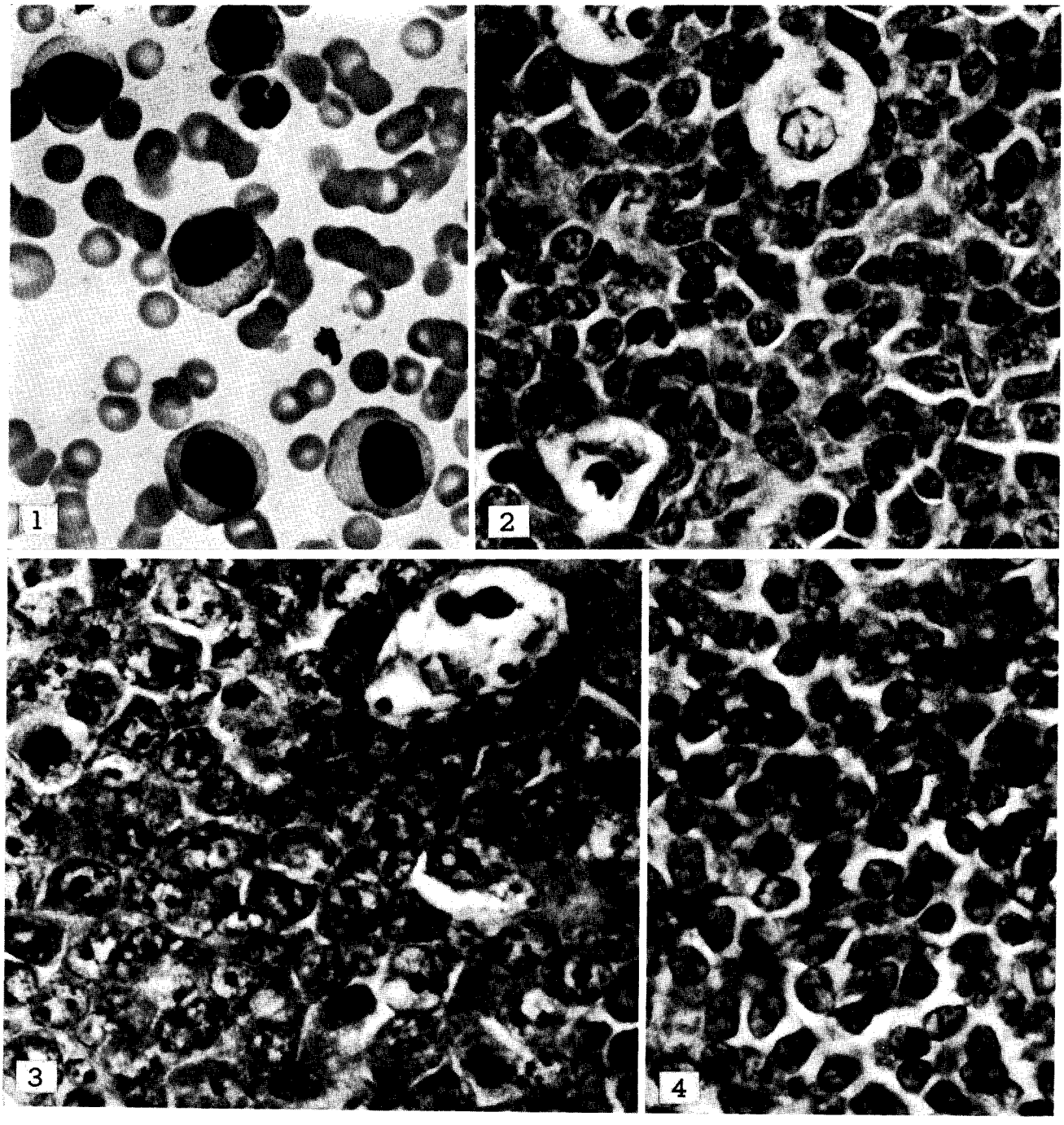
(*21*) SQUIRE RA: Comparative aspects of hematopoietic neoplasms of animals and man—summary. Natl Cancer Inst Monogr 32:363–365, 1969

(*22*) JONES SE, ROSENBERG SA, KAPLAN HS, et al: Non-Hodgkin's lymphomas. II. Single agent chemotherapy. Cancer 30:31–38, 1972

(*23*) CARBONE PP: Non-Hodgkin's lymphoma: Recent observations on natural history and intensive treatment. Cancer 30:1511–1516, 1972

(*24*) ROSENBERG SA: Report of the committee on the staging of Hodgkin's disease. Cancer Res 26:1310, 1966

(*25*) RAPPAPORT H: Tumors of the hematopoietic system. *In* Atlas of Tumor Pathology. Washington, D.C., Armed Forces Inst Pathol, 1966, pp 91–206



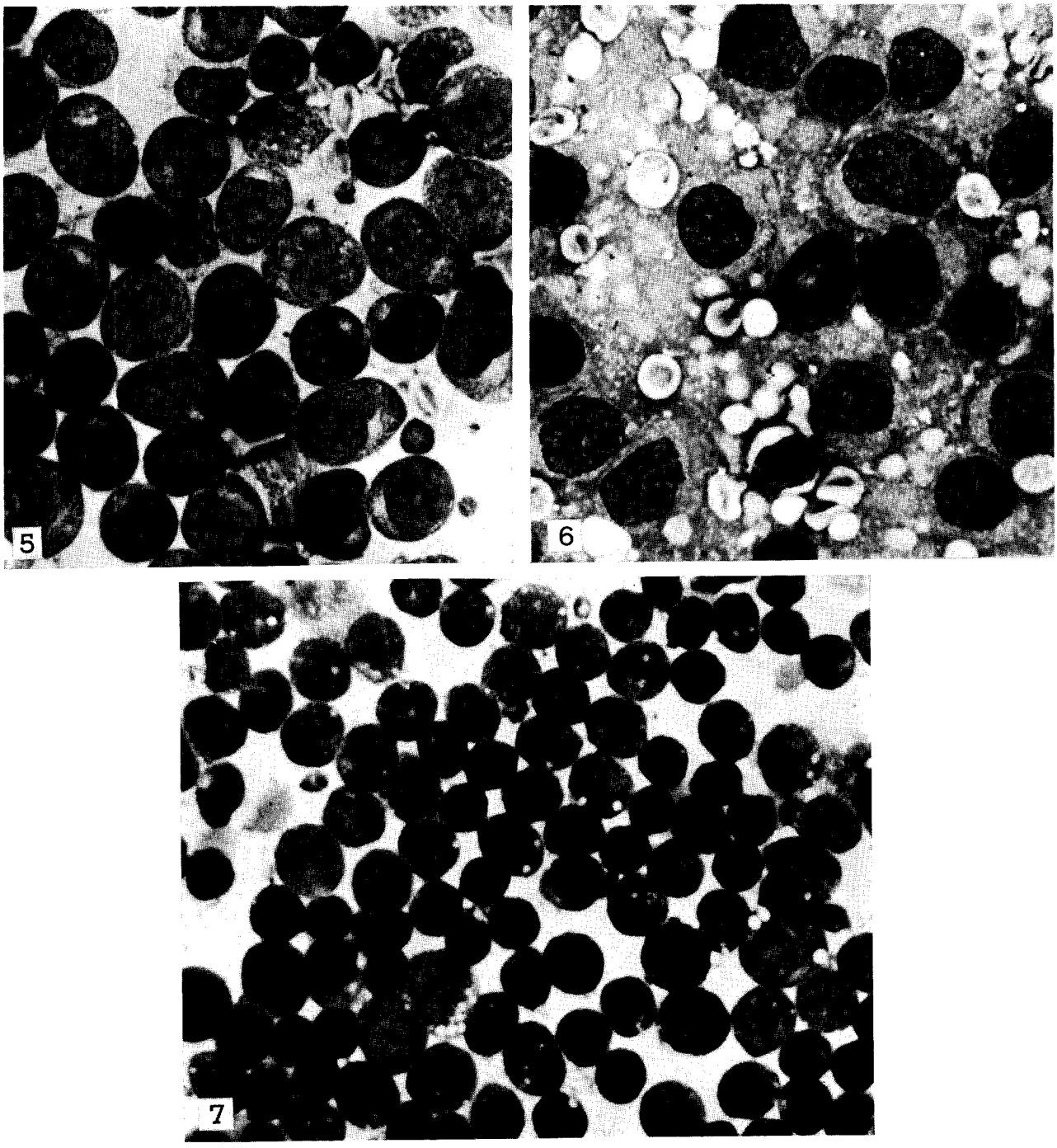
Canine lymphomas. × 1100

FIGURE 1.—Leukemic peripheral blood smear.

FIGURE 2.—Undifferentiated or stem-cell type.

FIGURE 3.—Histiocytic type.

FIGURE 4.—Lymphocytic poorly differentiated type.



Fresh imprints of canine lymphomas. × 1100

FIGURE 5.—Fine chromatin pattern.

FIGURE 6.—Stippled chromatin pattern.

FIGURE 7.—Coarse chromatin pattern.